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EXAMINER	
HARLE, JENNIFER I	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/076,213	Applicant(s) CHAN ET AL.	
	Examiner Jennifer I. Harle	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 17-33 are pending. Claims 1-16 have been previously cancelled.

Response to Amendment

Claim Objections/Status of the Claims

1. The examiner thanks Applicants' for the acknowledgment of the List of Claims, as reflecting the corrected numbering.

2. Claims 24 and 32 are objected to because of the following informalities: line 2 of both claims states "selected from the group consisting α-lactose..." – it should read "selected from the group consisting **of** α-lactose...". Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The rejection of claims 17-33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in light of Applicants' Amendments.

4. The rejection of claims 17 and 26 of the recititation of "DNAse" but failing to identify which DNAse is intended is withdrawn in light of Applicants' Amendment to "a human DNAse".

5. The rejection of claims 17 and 18 as confusing because it is not clear if the temperature step is required to minimize the aggregation or the aggregation is minimized in spite of the identified elevated temperature is withdrawn in light of Applicants' Amendments and comments which clarify that the temperature is required to minimize the aggregation.

6. The rejection of claims 19-22 and 28-30 as vague and indefinite because it is not clear if the DNAse containing solutes have the recited pH value, or these pH values are intended use is

withdrawn in light of Applicants' Amendments and comments which clearly indicate that the pH of the solution is below a certain value prior to the elevation of the temperature.

7. The rejection of claim 32 as an improper Markush Group is withdrawn in light of Applicants' Amendment.

8. The rejection of claim 33 a lacking clear antecedent basis because the process is directed to a method of making a solution and not a solid is withdrawn in light of Applicants' Amendment.

Claim Rejections - 35 USC § 102

9. The rejection of claims 17-19, 22-24, 26-28 and 31-33under 35 U.S.C. 102(b) as being anticipated by Heicke, et al. (1969) is withdrawn in light of Applicants' Amendment to a human DNAse as Heicke discloses a DNAse from a marine sponge *Veronigia aerophoba*.

10. The rejection of claims 17-19, 22, 24, 26-28 and 32-33under 35 U.S.C. 102(b) as being anticipated by Khouw, et al. (1969) is withdrawn in light of Applicants' Amendment to a human DNAse as Khouw discloses a DNAse from a bovine.

11. The rejection of claims 17-18, 23-24, 26-27 and 31-33 under 35 U.S.C. 102(b) as being anticipated by Karimov, et al. (1982) is withdrawn in light of Applicants' Amendment to a human DNAse as Karimov discloses pancreatic DNAse but does not disclose whether it is human or bovine and the temperature is never elevated above 37 degrees C.

Claim Rejections - 35 USC § 103

12. The rejection of claims 17-33 under 35 U.S.C. 103(a) as being unpatentable over Heicke, et al. (1969) in view of Arakaw, et al. (1982), Back, et al. (1979) and van de Beek, et al. (1969) is withdrawn in light of Applicants' Amendment to a human DNAse.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 17-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prestrelski,et al. (US 5,580,856) in view of Shak, et al. (WO 90/07572) and further in view of Frenz, et al. (WO 93/256670).

Prestrelski discloses that a process for decreasing the amount of aggregated protein upon reconstitution of a dried protein. Col. 2, lines 45-60. Prestelski notes that dried proteins are subject to conformational instability induced by acute stresses encountered during drying and that protein stability during drying is a function of environmental factors, which include temperature, humidity, pH, ionic strength, and solvent medium; while noting that damage to dried proteins is manifested after rehydration, for example as a loss of protein solubility, loss of activity in appropriate bioassays, aggregation, or in the case of enzymes, a loss of catalytic activity. Cols. 1-2. Prestrelski further notes that typical practices to improve protein stability are addressed by varying the formulation, i.e. excipients are added to the protein solution or suspension prior to drying to improve the stability of the protein or drying process, and to improve the storage stability of the dried product (common excipients include sugars, e.g. sucrose, glucose, lactose, trehalose, polyols – xylitol, mannitol, inositol, sorbitol). Cols. 1-2. However, Proestrelski discloses that while the use of additives has improved the stability of dried proteins many protein which are subject to drying and subsequent storage contain unacceptable or undesirable amounts of inactive, aggregated protein in the rehydrated formulation and that this

is particularly problematic when preparing pharmaceutical formulations because aggregated proteins have been known to be immunogenic. Col. 2, lines 19-37. Thus, Prestrelski discloses that a significant portion of the inactive proteins in formulations prepared from dried proteins can be the result of aggregation of otherwise undamaged protein upon reconstitution, i.e. during the rehydration step, and adding excipients which inhibit aggregation of otherwise undamaged protein, i.e. reconstitution stabilizers, which include osmolyes, i.e. polyols (sorbitol, mannitol, xylitol and glycerol), and sugars (trehalose, lactose, sucrose, etc.) in a concentration in the rehydration formulation between about 0.01 weight percent to 10 percent weight percent, buffers ranging in a pH from 1-13 depending upon the substances that maintain physiological or otherwise optimal pH, isotoncity and stability, and a reconstitution temperature, i.e. after the aggregating sugar has been added of 2-50 degrees C. Cols. 3-4. Prestrelski specifically discloses that the present invention may be applied to any protein subjected to freeze-drying or any other forms of drying such as spray-drying and air drying, including in the exemplary proteins DNAse I and DNAse II. Col. 6. Thus, Prestrelski discloses that the efficacy of an individual reconstitution stabilizer is protein dependent, but the selection and optimization of appropriate reconstitution stabilizers (as well as excipients in the pre-drying formulation) for a particular protein will be within the skill of ordinary artisans and obtainable with only routine experimentation and that the dried protein and an effective amount of the reconstitution stabilizer are admixed under conditions effective to reduce aggregation of the dried protein upon reconstitu8on with the reconstitution medium (e.g., a solvent and optionally other components (such as antibacterials) – the reconstitution stabilizer may be admixed with the dried protein at a suitable time before, during or after reconstitution; preferably the reconstitution stabilizer will be

pre-dissolved in the reconstitution medium and the dried protein is reconstituted at a temperature have the freezing point of the reconstitution medium, but which will not degrade the protein and will not be deleterious to the reconstitution stabilizer, preferably between 2-50 degrees C. Col. 7. In the specific examples of Prestrelski, lower pH at 4 and a temperature at 45 degrees C, after storage of two weeks showed better minimization of aggregation than higher pH at 7. Examples 1 and 2.

However, Prestrelski does not specifically disclose that the temperature is greater than 37 degrees C, the pH of the solution is below 7.0 or the sugar, whether it is alpha-lactose monhydrate, mannitol, trehalose or sucrose, is present in an amount from 50 mg/ml to 200 mg/ml or that this particular spray dried powder DNAse is therapeutically effective when administered to the lungs of an individual. Shak discloses that human DNAse can be used in lieu of bovine DNAse for pharmaceutical purposes and can be synthesized by *in vitro* methods or is obtained readily from human pancreatic cDNA libraries. Pp. 1-2 and 11. Shak additionally discloses that human DNAse is placed into therapeutic formulations together with required cofactors, and optionally is administered in the same fashion as has been the case for animal DNase such as bovine pancreatic DNase, i.e. liquid where the pH may range from 5.5-9.0 and buffers compatible with the included divalent cation may also be utilized, as well as lyophilized powder nebulized after reconstitution. Pp. 1-2 and 16-17. Shak further discloses that human DNase is particularly useful for the treatment of patient with pulmonary disease and is also use for adjunctive treatment for improved management of abscesses or severe closed-space infections in conditions such as empyema, meningitis, abscess, peritonitis, sinusitis, etc. as well as

maintaining the flow in medical conduits communicating with a body cavity, among other uses. Pg. 17.

Frenz discloses the use of purified forms of human DNAse, which can be spray-dried, as pharmaceutical compositions for use in administration to patients suffering from pulmonary distress. Abstract. Frenz further discloses that the optimum pH for storage of human DNAse in solution is 5.0-6.8, as deamidation of human DNase occurs at elevated pH as non-deamidated DNase is fully enzymatically active as compared with deamidated DNase. Pp. 2 and 18-19.

A person of ordinary skill in the art at the time the invention was made would have been motivated to use pH values between 7.0 and 5.0 and a temperature above 37 degrees C or above 60 degrees C in the protein/osmolyte solution of Pretselski, where the protein was DNAse and the osmolyte was a sugar, specifically mannitol, sucrose, trehalose because Pretselski clearly indicates that any protein (which would include human DNAse), which can be spray dried can be utilized in his invention and specifically mentions DNAse I and DNAse II and specifically mentions the osmolytes being the specific sugars to inhibit aggregation and Shak and Frenz specifically mention the use of human DNAse as a spray-dried pharmaceutical with pH values in the range for storage purposes and in the case of Frenz to prevent deamidation in order to keep the product enzymatically active. Moreover, optimization of the temperature to prevent aggregation of a protein including DNAses is taught by Pretselski and they are the same, i.e. human if not closely related, i.e. bovine.

Hence it would have been prima-facie obvious to one of ordinary skill in the art at the time of the invention to stabilize DNAse with sugars and/or pH values less than 7.0 and temperatures above 37 degrees C or 60 degrees C.

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chritopher Tate
Primary Examiner
Art Unit 1654

JIH/February 1, 2005